

Amendments to the Specification:

Please replace the paragraph beginning on page 7, line 9, with the following amended paragraph:

B1
Other anti-HER2 antibodies with various properties have been described in Tagliabue *et al.* *Int. J. Cancer* 47:933-937 (1991); McKenzie *et al.* *Oncogene* 4:543-548 (1989); Maier *et al.* *Cancer Res.* 51:5361-5369 (1991); Bacus *et al.* *Molecular Carcinogenesis* 3:350-362 (1990); Stancovski *et al.* *PNAS (USA)* 88:8691-8695 (1991); Bacus *et al.* *Cancer Research* 52:2580-2589 (1992); Xu *et al.* *Int. J. Cancer* 53:401-408 (1993); WO94/00136; Kasprzyk *et al.* *Cancer Research* 52:2771-2776 (1992); Hancock *et al.* *Cancer Res.* 51:4575-4580 (1991); Shawver *et al.* *Cancer Res.* 54:1367-1373 (1994); Arteaga *et al.* *Cancer Res.* 54:3758-3765 (1994); Harwerth *et al.* *J. Biol. Chem.* 267:15160-15167 (1992); U.S. Patent No. 5,783,186; Klapper *et al.* *Oncogene* 14:2099-2109 (1997); ~~WO 98/77797~~ WO 98/17797; and US Patent No. 5,783,186. Homology screening has resulted in the identification of two other ErbB receptor family members; HER3 (US Pat. Nos. 5,183,884 and 5,480,968 as well as Kraus *et al.* *PNAS (USA)* 86:9193-9197 (1989)) and HER4 (EP Pat Appln No 599,274; Plowman *et al.*, *Proc. Natl. Acad. Sci. USA*, 90:1746-1750 (1993); and Plowman *et al.*, *Nature*, 366:473-475 (1993)). Both of these receptors display increased expression on at least some breast cancer cell lines.

Please replace the paragraph beginning on page 9, line 14, with the following amended paragraph:

B2
Induction of various cellular responses mediated by such TNF family cytokines is believed to be initiated by their binding to specific cell receptors. Previously, two distinct TNF receptors of approximately 55-kDa (TNFR1) and 75-kDa (TNFR2) were identified (HohmanHohmann *et al.*, *J. Biol. Chem.*, 264:14927-14934 (1989); Brockhaus *et al.*, *Proc. Natl. Acad. Sci.*, 87:3127-3131 (1990); EP 417,563, published March 20, 1991; Loetscher *et al.*, *Cell*, 61:351 (1990); Schall *et al.*, *Cell*, 61:361 (1990); Smith *et al.*, *Science*, 248:1019-1023 (1990); Lewis *et al.*, *Proc. Natl. Acad. Sci.*, 88:2830-2834 (1991); Goodwin *et al.*, *Mol. Cell. Biol.*, 11:3020-3026 (1991)). Those TNFRs were

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found to share the typical structure of cell surface receptors including extracellular, transmembrane and intracellular regions. The extracellular portions of both receptors were found naturally also as soluble TNF-binding proteins (Nophar *et al.*, *EMBO J.*, 9:3269 (1990); and Kohno *et al.*, *Proc. Natl. Acad. Sci. U.S.A.*, 87:8331 (1990); Hale *et al.*, *J. Cell. Biochem. Supplement* 15F, 1991, p. 113 (P424)).

Please replace the paragraph beginning on page 9, line 25, with the following amended paragraph:

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The extracellular portion of type 1 and type 2 TNFRs (TNFR1 and TNFR2) contains a repetitive amino acid sequence pattern of four cysteine-rich domains (CRDs) designated 1 through 4, starting from the NH₂-terminus. (Schall *et al.*, *supra*; Loetscher *et al.*, *supra*; Smith *et al.*, *supra*; Nophar *et al.*, *supra*; Kohno *et al.*, *supra*; Banner *et al.*, *Cell*, 73:431-435 (1993)). A similar repetitive pattern of CRDs exists in several other cell-surface proteins, including the p75 nerve growth factor receptor (NGFR) (Johnson *et al.*, *Cell*, 47:545 (1986); Radeke *et al.*, *Nature*, 325:593 (1987)), the B cell antigen CD40 (Stamenkovic *et al.*, *EMBO J.*, 8:1403 (1989)), the T cell antigen OX40 (Mallet *et al.*, *EMBO J.*, 9:1063 (1990)) and the Fas antigen (Yonehara *et al.*, *supra* and Itoh *et al.*, *Cell*, 66:233-243 (1991)). CRDs are also found in the soluble TNFR (sTNFR)-like T2 proteins of the Shope and myxoma poxviruses (Upton *et al.*, *Virology*, 160:20-2920-30 (1987); Smith *et al.*, *Biochem. Biophys. Res. Commun.*, 176:335 (1991); Upton *et al.*, *Virology*, 184:370 (1991)). Optimal alignment of these sequences indicates that the positions of the cysteine residues are well conserved. These receptors are sometimes collectively referred to as members of the TNF/NGF receptor superfamily.

Please replace the paragraph beginning on page 10, line 9, with the following amended paragraph:

B4

More recently, other members of the TNFR family have been identified. In von Bulow *et al.*, *Science*, 278:138-141 (1997), investigators describe a plasma membrane receptor referred to as Transmembrane Activator and CAML-Interactor or "TACI". The TACI receptor is reported to contain a cysteine-rich motif characteristic of the TNFR family. In an *in vitro* assay, cross linking of TACI on the surface of transfected Jurkat

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B4Cone cells with TACI-specific antibodies led to activation of NF-KB (see also, WO 98/39361 published September 18¹¹, 1998).

Please replace the paragraph beginning on page 10, line 37, and ending on page 11, line 9, with the following amended paragraph:

B5 In Sheridan *et al.*, *Science*, 277:818-821 (1997) and Pan *et al.*, *Science*, 277:815-818 (1997), another molecule believed to be a receptor for Apo2L/TRAIL is described (see also, WO98/51793 published November 19, 1998; and WO98/41629 published September 24, 1998). That molecule is referred to as DR5 (it has also been alternatively referred to as Apo-2; TRAIL-R, TR6, Tango-63, hAPO8, TRICK2 or KILLER (Screaton *et al.*, *Curr. Biol.*, 7:693-696 (1997); Walczak *et al.*, *EMBO J.*, 16:5386-5387~~5386-5397~~ (1997); Wu *et al.*, *Nature Genetics*, 17:141-143 (1997); WO98/35986 published August 20, 1998; EP870,827 published October 14, 1998; WO98/46643 published October 22, 1998; WO99/02653 published January 21, 1999; WO99/09165 published February 25, 1999; and WO99/11791 published March 11, 1999). Like DR4, DR5 is reported to contain a cytoplasmic death domain and be capable of signaling apoptosis. The crystal structure of the complex formed between Apo2L/TRAIL and DR5 is described in Hymowitz *et al.*, *Molecular Cell*, 4:563-571 (1999).

Please replace the paragraph beginning on page 11, line 16, with the following amended paragraph:

B6 A further group of recently identified receptors are referred to as "decoy receptors," which are believed to function as inhibitors, rather than transducers of signaling. This group includes DcR1 (also referred to as TRID, LIT or TRAIL-R3) (Pan *et al.*, *Science*, 276:111-113 (1997); Sheridan *et al.*, *Science*, 277:818-821 (1997); McFarlane~~MacFarlane~~ *et al.*, *J. Biol. Chem.*, 272:25417-25420 (1997); Schneider *et al.*, *FEBS Letters*, 416:329-334 (1997); Degli-Esposti *et al.*, *J. Exp. Med.*, 186:1165-1170 (1997); and Mongkolsapaya *et al.*, *J. Immunol.*, 160:3-6 (1998)) and DcR2 (also called TRUNDD or TRAIL-R4) (Marsters *et al.*, *Curr. Biol.*, 7:1003-1006 (1997); Pan *et al.*, *FEBS Letters*, 424:41-45 (1998); Degli-Esposti *et al.*, *Immunity*, 7:813-820 (1997)), both

cell surface molecules, as well as OPG (Simonet *et al.*, *supra*; Emery *et al.*, *infra*) and DcR3 (Pitti *et al.*, *Nature*, 396:699-703 (1998)), both of which are secreted, soluble proteins.

Please replace the paragraph beginning on page 11, line 32, with the following amended paragraph:

As reviewed recently by Tewari *et al.*, TNFR1, TNFR2 and CD40 modulate the expression of proinflammatory and costimulatory cytokines, cytokine receptors, and cell adhesion molecules through activation of the transcription factor, NF- κ B (Tewari *et al.*, *Curr. Op. Genet. Develop.*, 6:39-44 (1996)). NF- κ B is the prototype of a family of dimeric transcription factors whose subunits contain conserved Rel regions (Verma *et al.*, *Genes Develop.*, 9:2723-2735 (1996)(1995); Baldwin, *Ann. Rev. Immunol.*, 14:649-681(649-683 (1996)). In its latent form, NF- κ B is complexed with members of the I- κ B inhibitor family; upon inactivation of the I- κ B in response to certain stimuli, released NF- κ B translocates to the nucleus where it binds to specific DNA sequences and activates gene transcription. As described above, the TNFR members identified to date either include or lack an intracellular death domain region. Some TNFR molecules lacking a death domain, such as TNFR2, CD40, HVEM, and GITR, are capable of modulating NF- κ B activity. (see, *e.g.*, Lotz *et al.*, *J. Leukocyte Biol.*, 60:1-7 (1996)).

Please replace the paragraph beginning on page 13, line 1, with the following amended paragraph:

CD19 is another antigen that is expressed on the surface of cells of the B lineage. Like CD20, CD19 is found on cells throughout differentiation of the lineage from the stem cell stage up to a point just prior to terminal differentiation into plasma cells (Nadler, L. *Lymphocyte Typing II* 2: 3-37 and Appendix, Renling *et al.* eds. (1986) by Springer Verlag). Unlike CD20 however, antibody binding to CD19 causes internalization of the CD19 antigen. CD19 antigen is identified by the HD237-CD19 antibody (also called the "B4" antibody) (Kiesel *et al. Leukemia Research H*, 1211(12): 1119 (1987)), among others. The CD19 antigen is present on 4-8% of peripheral blood

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mononuclear cells and on greater than 90% of B cells isolated from peripheral blood, spleen, lymph node or tonsil. CD19 is not detected on peripheral blood T cells, monocytes or granulocytes. Virtually all non-T cell acute lymphoblastic leukemias (ALL), B cell chronic lymphocytic leukemias (CLL) and B cell lymphomas express CD19 detectable by the antibody B4 (Nadler *et al. J. Immunol.* 131:244 (1983); and Nadler *et al. in Progress in Hematology* Vol. XII pp. ~~187-206~~187-225. Brown, E. ed. (1981) by Grune & Stratton, Inc).

Please replace the paragraph beginning on page 13, line 17, with the following amended paragraph:

B9

The rituximab (RITUXAN®) antibody is a genetically engineered chimeric murine/human monoclonal antibody directed against the CD20 antigen. Rituximab is the antibody called "C2B8" in US Patent No. 5,736,137 issued April 7, 1998 (Anderson *et al.*). RITUXAN® is indicated for the treatment of patients with relapsed or refractory low-grade or follicular, CD20 positive, B cell non-Hodgkin's lymphoma. *In vitro* mechanism of action studies have demonstrated that RITUXAN® binds human complement and lyses lymphoid B cell lines through CDC (Reff *et al. Blood* 83(2):435-445 (1994)). Additionally, it has significant activity in assays for ADCC. More recently, RITUXAN® has been shown to have anti-proliferative effects in tritiated thymidine incorporation assays and to induce apoptosis directly, while other anti-CD19 and CD20 antibodies do not (Maloney *et al. Blood* 88(10):637a (1996)). Synergy between RITUXAN® and chemotherapies and toxins has also been observed experimentally. In particular, RITUXAN® sensitizes drug-resistant human B cell lymphoma cell lines to the cytotoxic effects of doxorubicin, CDDP, VP-16, diphtheria toxin and ricin (Demidem *et al. Cancer Chemotherapy Biotherapy & Radiopharmaceuticals* 12(3):177-186 (1997)). *In vivo* preclinical studies have shown that RITUXAN® depletes B cells from the peripheral blood, lymph nodes, and bone marrow of cynomolgus monkeys, presumably through complement and cell-mediated processes (Reff *et al. Blood* 83(2):435-445 (1994)).